JOURNAL OF CLINICAL ONCOLOGY

Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead

Véronique Minard-Colin, Laurence Brugières, Alfred Reiter, Mitchell S. Cairo, Thomas G. Gross, Wilhelm Woessmann, Birgit Burkhardt, John T. Sandlund, Denise Williams, Marta Pillon, Keizo Horibe, Anne Auperin, Marie-Cécile Le Deley, Martin Zimmerman, Sherrie L. Perkins, Martine Raphael, Laurence Lamant, Wolfram Klapper, Lara Mussolin, Hélène A. Poirel, Elizabeth Macintyre, Christine Damm-Welk, Angelo Rosolen, and Catherine Patte

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on August 24, 2015.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Catherine Patte, MD, Department of Pediatric Oncology, Gustave Roussy, 114 Rue Paul Vaillant, 94800 Villejuif, France; e-mail: catherine.patte@gustaveroussy.fr.

A B S T R A C T

Non-Hodgkin lymphoma is the fourth most common malignancy in children, has an even higher incidence in adolescents, and is primarily represented by only a few histologic subtypes. Dramatic progress has been achieved, with survival rates exceeding 80%, in large part because of a better understanding of the biology of the different subtypes and national and international collaborations. Most patients with Burkitt lymphoma and diffuse large B-cell lymphoma are cured with short intensive pulse chemotherapy containing cyclophosphamide, cytarabine, and high-dose methotrexate. The benefit of the addition of rituximab has not been established except in the case of primary mediastinal B-cell lymphoma. Lymphoblastic lymphoma is treated with intensive, semi-continuous, longer leukemia-derived protocols. Relapses in B-cell and lymphoblastic lymphomas are rare and infrequently curable, even with intensive approaches. Event-free survival rates of approximately 75% have been achieved in anaplastic large-cell lymphomas with various regimens that generally include a short intensive B-like regimen. Immunity seems to play an important role in prognosis and needs further exploration to determine its therapeutic application. ALK inhibitor therapeutic approaches are currently under investigation. For all pediatric lymphomas, the intensity of induction/consolidation therapy correlates with acute toxicities, but because of low cumulative doses of anthracyclines and alkylating agents, minimal or no long-term toxicity is expected. Challenges that remain include defining the value of prognostic factors, such as early response on positron emission tomography/computed tomography and minimal disseminated and residual disease, using new biologic technologies to improve risk stratification, and developing innovative therapies, both in the first-line setting and for relapse.

J Clin Oncol 33:2963-2974. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies. The histologic classification of these diseases has changed many times over the years as a result of better understanding of lymphomagenesis and development of new diagnostic tools. The 2008 WHO classification of lymphoma is now widely used, providing clinicians with a common language and valuable comparisons.[1] NHL is the fourth most common malignancy across the pediatric age spectrum. Pediatric NHL exhibits significant differences in the distribution of histologic subtypes to NHL observed in adults with clinical features characterized by almost exclusively diffuse high-grade lymphomas and frequent extranodal involvement. Dramatic progress has been achieved in developing curative therapy for pediatric NHL, with an overall survival rate now exceeding 80%. Because of the relatively small numbers of each subtype, such progress could not have been achieved without national and international collaborations especially through the European Intergroup for Childhood NHL (EICNHL), which comprises most European countries, Japan and Hong Kong, and the North American Children's Oncology Group (COG). This review will present current knowledge on pediatric NHL and identify future research directions, especially in terms of biology and new therapies.

GENERALITIES

Epidemiology and Histopathology

The overall incidence and frequency of the different histologic subgroups of NHL vary according

to age at diagnosis. Data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results program have demonstrated a steady increase in NHL with age. The annual incidence per million inhabitants ranges from 5.9 in children younger than 5 years of age to about 10 in children between 5 and 14 years old, and 15 in adolescents (approximately 150 in adults).[2] The increased incidence in adolescents is related to the higher incidence of large-cell lymphomas at that age. The vast majority of childhood NHL is high-grade lymphoma, mostly of B-cell origin (Table 1).[1,3,4] Other subtypes, such as peripheral T-cell lymphoma, extranodal natural killer/T–cell lymphoma, and follicular lymphoma, represent less than 5% of all pediatric NHL.

It is well known that immunodeficiency, either primary (such as ataxia telangiectasia or Nijmegen breakage syndrome) or secondary (induced by HIV or immunosuppressive drugs), increases the risk of NHL.[5,6] Less known and more recently described are the association of interleukin (IL) -10 receptor deficiency with childhood B-cell NHL (B-NHL)[7] and the increased risk of NHL in the constitutional mismatch repair deficiency syndrome. The latter is characterized by biallelic germline mutations of mismatch repair genes and multiple cancers including NHL, brain tumors, and colorectal cancers in children with café au lait spots.[8]

Staging

The Ann Arbor classification is not adapted to childhood NHL because of its predominant involvement in extranodal primary sites. The commonly used St Jude staging classification designates mediastinal and extensive abdominal lesions as stage III and restricts stage IV assignment to bone marrow (BM) and CNS involvement regardless of involvement of other visceral sites. The International Prognostic Index is not used in childhood NHL because of the difference in staging and because the performance status index does not reflect quality-of-life deterioration but rather rapidity of tumor growth and tumor volume. The role of fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in the management of childhood NHL has yet to be established. PET-FDG may be more accurate than conventional imaging to assess disease involvement because high FDG uptake has been shown in most subtypes (Abbou et al, submitted for publication), but its impact on therapeutic stratification has not been evaluated. The role of FDG-PET in remission assessment has only been investigated in small series. Most reports indicate high rates of false-positive results, requiring histologic examination of residual masses before treatment modification (Abbou et al, submitted for publication). Lastly, the prognostic value of early (after one to three cycles of chemotherapy) FDG-PET/CT response assessment has

Table 1. Immunophenotypic, Cytogenetic, and Molecular Markers of Pediatric NHL						
	Histology and Frequency					
		LBCL (10%-15%)		LL (20%-25%)		
Marker	BL (50%-60%)	DLBCL	PMBL	B-LL	T-LL	ALCL (10%-12%)
Immunohistochemistry*						
MIB1	~100%	40%-90%	30%-90%	Not informative	Not informative	Not informative
CD10	+	+/−	−/+	+/−	+/−	−
CD19	+	+	+	+	−	−
CD20	+	+	+	+/−	−	−
CD79a	+	+	+	+	−	−
sIg	+	+/−	−	−	−	−
Bcl-6	+	+/−	+/−	−	−	+/−
MUM1	−	−/+	+	−	−	−
MAL	−	−/+	+	−	−	−
TdT	−	−	−	+	+	−
cCD3	−	−	−	−	+	−/+
CD4	−	−	−	−	+/−	−/+
CD8	−	−	−	−	+/−	−/+
CD7	−	−	−	−	+	−/+
CD5	−	−/+	−	−	+/−	+/−
CD30	−	†	+/−	−	−	+
ALK	−	‡	−	−	−	+
Cytogenetic	t(8;14)(q24;q32) t(2;8)(p12;q24) t(8;22)(q24;q11)	R8q24 (~30%)	Few data	Few data	Translocations involving 14q11-13; few other data	t(2;5)(p23;q35) > 90% or variants involving 2p23
Molecular biology	*MYC/IGH* *IGK/MYC* *MYC/IGL*		Nuclear factor-κB pathway dysregulation	*IGH/TCR* rearrangements	*NOTCH/FBXW7*, *PTEN* *IGH/TCR* rearrangements	*NPM/ALK* > 90% or variants

NOTE. Other NHLs, such as peripheral T-cell lymphoma, extranodal natural killer/T–cell lymphoma, nasal type, and pediatric follicular lymphoma, represent less than 5% of pediatric NHLs and are not indicated in the table.
Abbreviations: ALCL, anaplastic large-cell lymphoma, ALK positive; BL, Burkitt lymphoma; B-LL, B-cell lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; PMBL, primary mediastinal (thymic) large B-cell lymphoma; T-LL, T-cell lymphoblastic lymphoma.
*+, > 90% of patients; +/−, > 50% of patients; −/+, < 50% of patients; −, < 10% of patients.
†Positive especially in the rare anaplastic variant.
‡Positive in the ALK-positive LBCL.

also not been established. A prospective study is ongoing in France since 2011 for B-NHL, lymphoblastic lymphoma (LL), and anaplastic large-cell lymphoma (ALCL) to evaluate the role of FDG-PET/CT in pediatric NHL (ID-RCB: 2010-A01154-35).

Several groups have investigated the prognostic impact of minimal disseminated disease (MDD) at diagnosis identified by molecular techniques or flow cytometry in the blood, BM, and/or CNS.[9-11] Recently, a multidisciplinary multinational group proposed a Revised International Pediatric NHL Staging System Classification and International Pediatric Non-Hodgkin lymphoma Response Criteria for improved staging and response assessments.[11a,11b]

Treatment

At the beginning of the 1980s, investigators contended that the type of multiagent chemotherapy should differ according to the NHL histology based on clinical experiences. A Children's Cancer Group randomized study showing that LL benefited from a 10-drug leukemia-like LSA_2L_2 protocol and that non-LL had better outcomes with a four-drug cyclophosphamide, vincristine, methotrexate (MTX), and prednisone regimen confirmed these perceptions.[12] Since 1981, national groups have conducted prospective trials with different strategies, including essential CNS prophylaxis, for B-NHL and LL that significantly advanced cure rates in these diseases.

MATURE B-CELL LYMPHOMA

Burkitt lymphoma (BL) accounts for more than 80% of childhood B-NHL. It generally arises in the abdomen and/or head and neck region and presents as advanced-stage disease involving the BM and/or CNS in approximately 20% to 25% of patients. Outcomes have improved dramatically as a result of several consecutive prospective trials, such as the French Society of Pediatric Oncology and French-American-British (FAB) Lymphomes Malins B (LMB) and the oligonational Berlin-Frankfurt-Munster (BFM) studies (Table 2).[4,13-20] Treatment of BL is based on 2 to 6 months of intensive pulse polychemotherapy. Relapses occur early, typically within the first year. The LMB studies,[13,14] including the international FAB/LMB96 trial,[15-17,21] sequentially demonstrated that high-dose (HD) MTX is an effective drug for CNS prophylaxis; patients with mature B-cell acute leukemia and CNS-positive disease benefit from a higher dose of HDMTX and the addition of HD cytarabine (Ara-C [in cytarabine/etoposide (CYVE) courses]); treatment intensity should be based on tumor resectability, stage, and response to chemotherapy (at day 7 and after three courses); early dose-intensity is essential as evident by a 10% lower event-free survival (EFS) in the intermediate-risk group of the FAB/LMB96 trial when the second induction course started later than 21 days after the first one; and the total dose of cyclophosphamide and doxorubicin could be reduced to 3.3 g/m^2 and 120 mg/m^2, respectively, for more than 70% of patients, substantially reducing the risk of gonadal and cardiac toxicity. The BFM studies[4,18,19] showed that treatment intensity can be adapted to the lactate dehydrogenase (LDH) level; HDMTX is an effective systemic drug; and advanced disease benefits from more prolonged HDMTX exposure and HDAra-C. Although stratification and the therapy intensity are not exactly comparable in the LMB and BFM strategies, the results are quite similar. Other studies also showed the value of short-duration therapy and confirmed that cyclophosphamide, HDMTX, and Ara-C are the ma-

jor drugs in BL, in addition to vincristine, doxorubicin, etoposide, and corticosteroids.[20] Collectively, all studies established the effectiveness of CNS prophylaxis with HDMTX $\pm$ HDAra-C and intrathecal (IT) injections of MTX $\pm$ Ara-C, eliminating the need for cranial irradiation. In higher income countries, the EFS of BL reaches 80% to 90% using these strategies; however, acute treatment-related toxicities necessitate adequate supportive care and protocol management experience (Table 2).[15-17,19-21]

BL frequently occurs in countries with fewer resources, especially in sub-Saharan countries. Treatment should be adapted to find a compromise between sufficient effectiveness, tolerable toxicity, and socioeconomic constraints. Several groups have published results demonstrating cure in about half of the children with resource-adapted protocols.[22,23] These cure rates should improve with experience, better resources, and less family abandonment of treatment.

Diffuse large B-cell lymphoma (DLBCL) accounts for 10% to 20% of B-cell lymphoma in children and occurs more frequently in adolescents.[24] DLBCL in children is more homogeneous than in adults, with the majority originating from germinal centers (germinal center B-cell–like [GCB]), possibly representing a distinct biologic subgroup of GCB devoid of *BCL6*/3q27 and *BCL2*/18q21 translocations.[25,26] *MYC*/8q24 is frequently rearranged (20% to 30%), in contrast to adult DLBCL (5% to 10%).[27] Outcomes in children and adolescents are similar to those of BL with the same protocols except that relapses have been reported up to 3 years after diagnosis.[14,18,20]

The subgroup of primary mediastinal large B-cell lymphoma (PMBL) has to be distinguished from other DLBCL.[19,27,28] Using BL pediatric protocols, EFS is lower than in DLBCL (70%), but similar to that obtained with adult protocols. PMBL biology is similar in both age groups (although gray zone lymphoma with features intermediate between DLBCL and classical Hodgkin lymphoma is infrequently seen in children),[29] suggesting that rituximab-containing treatment regimens may improve outcomes as seen in adults.

The use of rituximab in pediatric B-NHL remains a relevant clinical question. Pilot studies have yielded responses for single-drug use in newly diagnosed BL[30] and immediate good tolerance when combined with induction chemotherapy.[31,32] However, considering the high cure rates obtained in children and adolescents with anticipated no or minimal long-term toxicity, the benefit of adding rituximab to conventional chemotherapy in BL has yet to be established. The ongoing Inter-B-NHL Ritux 2010 international trial combines a randomized phase III study testing the impact of adding rituximab to the LMB regimen for advanced-stage B-cell lymphoma and a phase II study of the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab regimen for PMBL[33] (ClinicalTrials.gov identifier: NCT01516580; Table 2).

Clinical prognostic factors observed in previous B-NHL studies include stage; LDH level; CNS involvement, especially the presence of blasts in the cerebrospinal fluid; and treatment-related factors such as early response, initial dose-intensity, and complete response (CR). Biologic characteristics also seem to have prognostic value, including the presence of 13q abnormalities, *MYC*/8q24 rearrangement in DLBCL, and MDD and minimal residual disease (MRD) in BL.[9,27,34] These results require confirmation in larger prospective studies, as planned in the Inter-B-NHL Ritux 2010 study.

Relapses in B-NHL are rare, but their outcome is dismal, with a cure rate of less than 30%.[35-37] CYVE[38] and rituximab, ifosfamide,

Table 2. Characteristics and Results of Main Studies in Childhood (< 18 years of age) B-Cell Lymphoma

Protocol	Study Groups	Randomization	Criteria for Stratification and Risk Groups	No. of Patients (%)	3- or 5-Year EFS (%)	No. of Courses	CNS Prophylaxis MTX (g/m²) and Infusion Duration	TD Cyclophosphamide (g/m²)	TD Ifosfamide (g/m²)	TD Doxorubicin (mg/m²)	TD Etoposide (g/m²)
LMB89[14]	SFOP	No	Stage, resection, CNS, response at day 7	561	91%						
			A: stage I and II resected	52 (9%)	98%	2	No	3		120	0
			B: not A not C	386 (69%)	92%	5	5 HDMTX = 3 g/m² (3 hours), 10 DIT	5.3		180	0
			C: CNS involvement and/or BM > 70%	123 (22%)	84% (no CNS involvement, 90%; CNS involvement, 79%)	8	5 HDMTX = 8 g/m² (4 hours), 2 HDAra-C (CYVE), 10 TIT	6.8		240	2.5
FAB/LMB96[15-17]	SFOP	Yes	Idem LMB89	1,111	88%						
	UKCCSG	Yes	A: idem LMB89	132 (12%)	99%	2	No	3		120	0
	CCG	Yes	B: not A not C	744 (67%)	89%	4	Idem LMB89	3.3*		120*	0
		Yes	C: CNS involvement, BM > 25%	235 (21%)	79%	8	Idem LMB89	6.8*		240*	2.5
BFM90[18]	BFM	No	Resection, site, LDH (500 IU/L), BM, CNS	413	88%						
			R1: complete resection	71 (17%)	100%	2	2 MTX 0.5 g/m² (24 hours), 3 TIT	2	4	50	0.2
			R2: extra-abdominal only or abdominal and LDH < 500 IU/L	167 (40%)	96%	4	4 HDMTX 5 g/m² (24 hours), 5 TIT	3	8	100	0.4
			R3: abdominal and LDH > 500 IU/L and/or CNS involvement, and/or BM positive, and/or multifocal bone	175 (43%)	79% (CNS involvement, 65%)	6	6 HDMTX 5 g/m² (24 hours), 7 TIT	4	12	150	0.6
BFM95[19]	BFM	Yes	Resection, stage, CNS, LDH (< 500, 500-1,000, > 1,000 IU/L) Random: HDMTX 4 h v 24 h	505	89%						
		Yes	R1: stage I and II resected	48 (10%)	94%	2	2 HDMTX 1 g/m² (4 hours),* 3 TIT	2	4	50	0.2
		Yes	R2: stage I and II nonresected, stage III and LDH < 500 IU/L	233 (46%)	94%	4	4 HDMTX 1 g/m² (4 hours),* 5 TIT	2.4	8	100	0.4
		Yes	R3: stage III and LDH < 1,000 IU/L, stage IV/B-AL and LDH < 1,000 IU/L	82 (16%)	85%	5	4 HDMTX 5 g/m² (24 hours), 1 HDAra-C (CC), 6 TIT	2.4	8	100	0.9
		Yes	R4: LDH > 1,000 IU/L, CNS involvement	142 (28%)	81% (CNS involvement, 69%)	6	4 HDMTX 5 g/m² (24 hours), 2 HDAra-C, 7 TIT	2.4	8	100	1.4
B-NHL03[20]	JPLSG	No	Stage, resection, BM, CNS	321	87%						
			G1: stage I and II resected	17	94%	2	2 DIT	1.5		120†	0
			G2: stage I and II nonresected	103	99%	4	2 TIT, 2 DIT, 2 HDMTX 3 g/m² (24 hours), 2 MTX 0.5 g/m² (6 hours)	1.5		120†	0
			G3: stage III and IV, no CNS involvement	111	84%	6	4 TIT, 2 DIT, 4 HDMTX 3 g/m² (24 hours), 2 MTX 0.5 g/m² (6 hours)	3		240†	0.6
			G4: stage IV, CNS involvement, and B-AL	90	78%	6	6 TIT, 2 DIT, 4 HDMTX 5 (24 hours), 2 HDAra-C	5.5		240†	0.9

(continued on following page)

Table 2. Characteristics and Results of Main Studies in Childhood (< 18 years of age) B-Cell Lymphoma (continued)

Protocol	Study Groups	Randomization	Criteria for Stratification and Risk Groups	No. of Patients (%)	3- or 5-Year EFS (%)	No. of Courses	CNS Prophylaxis MTX (g/m²) and Infusion Duration	TD Cyclophosphamide (g/m²)	TD Ifosfamide (g/m²)	TD Doxorubicin (mg/m²)	TD Etoposide (g/m²)
Inter-B-NHL Ritux 2010 (ClinicalTrials.gov identifier: NCT01516580)	Part of EICNHL and COG	Yes	Stage, LDH > 2N, CNS, CSF; random assignment: with or without rituximab	600 planned	Study ongoing (NCT01516580)						
		Yes	B high: stage III and LDH > 2N, stage IV and no CNS involvement			4	5 HDMTX = 3 g/m² (3 hours), 10 DIT	3.3		120	0
		Yes	C1: stage IV and CNS involvement, B-AL, and CSF negative			6	3-4 HDMTX = 8 g/m² (4 hours), 2 HDAra-C (CYVE), 10-12 TIT	5.8		180	1.6
		Yes	C3: CSF positive			6	4 HDMTX = 8 g/m² (24 hours), 2 HDAra-C (CYVE), 12 TIT	5.8		180	1.6
		No	PMBL: PMBL, no CNS involvement, DA-EPOCH-R regimen	40 planned		6		> 6		> 240	> 1.2

Abbreviations: B-AL, mature B-cell acute leukemia; BFM, Berlin-Frankfurt-Munster; BM, bone marrow; BM > 70%, bone marrow involvement with more than 70% blasts; CC, combination of HDAra-C with etoposide and vindesine; CCG, Children's Cancer Group; COG, Children's Oncology Group; CSF, cerebrospinal fluid; CYVE, combination of cytarabine in continuous infusion and HDAra-C with etoposide; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with rituximab; DIT, double intrathecal injection (two drugs injected, either MTX or cytarabine with corticosteroid); EFS, event-free survival; EICNHL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB French-American-British; HDAra-C, high-dose cytarabine; HDMTX, high-dose methotrexate (with folinic rescue); JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group; LDH, lactate dehydrogenase; LDH > 2N, LDH level more than twice the institutional normal value; LMB, Lymphoma Malin B; MTX, methotrexate; PMBL, primary mediastinal B-cell lymphoma; SFOP, Société Francaise d'Oncologie Pédiatrique; TD, total (cumulative) dose; TIT, triple intrathecal injection (corticosteroids, MTX, cytarabine); UKCCSG, United Kingdom Children's Cancer Study Group.
*As results of the random assignments, these are the doses and the MTX infusion durations that are the standards in the current protocols.
†Pirarubicin instead of doxorubicin.

carboplatin, and etoposide[39] regimens are effective reinduction chemotherapy in achieving a second CR, with CR rates of 45%[37,38] and 35%,[39] respectively. HD chemotherapy and hematopoietic cell support are needed to consolidate the second CR. An allograft does not afford more benefit than an autograft,[40] but the former could be considered to maintain dose-intensity and/or in case of leukemic involvement. Adverse prognostic factors at relapse include early relapse (within 6 months), multiple sites of recurrence, BL histology, and initial presentation features (eg, elevated LDH and advanced-stage disease).[35-37]

Innovative therapies are difficult to explore in childhood B-NHL because of the small number of patients with refractory/relapsed disease. The most promising therapies include new antibody therapies along with immunomodulatory agents that improve antibody-coated tumor cell killing and Bruton's tyrosine kinase inhibitors. New monoclonal antibodies targeting B-cell markers such as next-generation humanized anti-CD20, obinutuzumab (GA101), or veltuzumab (IMMU-106) may be active, but none have been investigated in relapsed/refractory childhood B-NHL. Other new agents include the bi-specific CD20/CD22 or CD20/CD74 antibodies and the bi-specific CD19/CD3 T-cell engager blinatumomab (AMG103), with a reported response rate of approximately 55% among adults with relapsed aggressive B-NHL.[41] Another promising agent is ibrutinib, a potent oral inhibitor of Bruton's tyrosine kinase, which has a direct effect on malignant B cells and may also regulate the tumor B-cell microenvironment. Ibrutinib has demonstrated single-drug activity in relapsed/refractory B-cell malignancies in adults and has recently been reported to have a favorable tolerance profile and efficacy when combined with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in a nonrandomized study of newly diagnosed adult DLBCL (mostly post–germinal center disease).[42] Thus, ibrutinib could be a novel targeted therapy for relapsed/refractory childhood B-NHL in combination with a chemo-immunotherapy backbone.

Technologies such as next-generation sequencing, microRNA and gene expression profiling, and single nucleotide polymorphism array analysis may identify novel therapeutic targets. In BL, genetic alterations other than the 8q24/MYC translocation participate in the deregulation of the MYC pathway and may be essential for disease initiation and progression. Recurrent mutations in the PI3K pathway suggest a cooperative role between MYC overexpression and deregulation of PI3K signaling.[43] Other studies highlight the pathogenic and clinical relevance of mutations affecting the transcription factor TCF3 (E2A) or its negative regulator ID3, a novel tumor suppressor gene, with TCF3 or ID3 mutations affecting nearly 70% of sporadic BL.[44-46] In addition, mutations in genes including CCND3, GNA13, TP53, and SMARCA4 have been described. Interestingly, a comparison between the frequency of mutations in BL and adult GCB DLBCL revealed a stronger overlap, further supporting the notion that BL and GCB DLBCL both originate from germinal center B cells.[47] Altogether, these findings support the development of drugs targeting the PI3K kinase pathway, antigen-independent BCR signaling, and cyclin D3/CDK6 pathways in relapsed/refractory childhood B-NHL.

LL

LL includes both precursor T-cell (T-LL) and B-cell (B-LL) NHL. Unlike acute lymphoblastic leukemia (ALL), with predominant B-cell diseases, most LL is of T-cell origin, rather than B-cell origin (80% to 90% v 10% to 20%, respectively). T-LL generally presents with mediastinal and advanced-stage disease (stage III or IV in > 90% of patients) and may involve BM (approximately 30%) and less often CNS (approximately 5%) at diagnosis. B-LL is more likely to involve the skin, soft tissue, bone, and peripheral lymph nodes and represents the majority of the localized stages.[48]

Both precursor B- and T-lymphoid blasts usually express terminal deoxynucleotidyl transferase (TdT). TdT expression is the best immunohistochemical marker for determining the precursor origin of the neoplasm.[49] This is useful for differentiating B-LL from mature B-NHL, because they can express other similar markers (CD79a, CD10, and CD19 and/or CD20; Table 1).

The best treatment approaches for childhood advanced LL are ALL-based therapeutic regimens (eg, LSA$_2$L$_2$[50] and BFM[4,51,52] regimens). These protocols were modified by adding HDMTX to the original LSA$_2$L$_2$ protocol to improve CNS prophylaxis[53] and by gradually excluding local and CNS radiotherapy.[52,54] Regimens are based on semi-continuous intensive polychemotherapy followed by maintenance therapy for a total duration of 2 years (Table 3).[4,11b,52,53,55-63] Numerous drugs are given including corticosteroids, vincristine, anthracyclines, cyclophosphamide, Ara-C, asparaginase, and MTX. Several studies have demonstrated significance of asparaginase and its dose-intensity in LL outcomes.[62,63] CNS prophylaxis, another important component of treatment, generally involves HDMTX and/or IT injections. The randomized Pediatric Oncology Group[56] and COG[60] studies investigated the importance of HDMTX in LL. CNS prophylaxis with either sufficient number of IT injections or HDMTX prevented CNS relapse. In contrast to BL, these studies suggested that HDMTX may not have as profound a systemic effect in LL. Other protocols introduced early intensification to BFM-like regimens to produce more rapid disease response, but this approach did not improve long-term outcome.[60,62]

Of note, outcomes for pediatric LL have not changed significantly since the 1980s, with most clinical trials achieving EFS rates of 75% to 85% (Table 3). The BFM90 study, which attained a 90% EFS rate, represents the only exception, but this result was not reproduced in the subsequent BFM95 study.[52] Despite minimal differences between the two protocols, the divergent results obtained may be explained by a different dose and type of asparaginase. To date, except for stage (localized v advanced), no clinical prognostic factors have been identified.[51,64] A trend toward a better prognosis was shown in patients with a very good response after the 7-day prephase of corticosteroids[54] or with a radiologic response at 2 weeks.[60] The EICNHL group designed the Euro-LB02 trial to compare dexamethasone (known to better penetrate the CNS) to prednisone in the induction phase and evaluate the possibility of decreasing the duration of treatment from 24 to 18 months (second random assignment). The reference arm was the NHL-BFM90 regimen without cranial irradiation, and only patients with T-LL were randomly assigned. The study had to be closed prematurely because of excess toxic deaths. Preliminary results[61] showed an EFS rate of 81% ± 2% for the 319 eligible patients (75% T-LL) with a median follow-up of 4.8 years. Although no CNS relapses occurred in the dexamethasone arm, survival was not better.

Because of relevant acute and long-term toxicity and poor prognosis at relapse, identifying prognostic factors is an important challenge in LL. This has been hampered by the rarity of the disease and,

Table 3. Characteristics and Results of Main Series of Pediatric Lymphoblastic Lymphoma (series of localized diseases or B-LL are not presented)

Protocol	Study Group and Period of Study	Study Patients	Treatment Strategy	Treatment Duration (months)	RT	CNS Prophylaxis	No. of Patients With LL	3- to 5-Year EFS (%)	3- to 5-Year OS (%)
CCG-551[12] (COMP v LSA$_2$L$_2$)	CCG, 1977-1982	NHL	LSA$_2$L$_2$	18	Local	IT	124 (stages III and IV)	64	67
LSA$_2$L$_2$[50]	MSKCC, 1971-1990	LL, all stages	LSA$_2$L$_2$	24-36	Local	IT	95 (80% T-LL)	75	79
LMT81[53]	IGR, 1981-1989	LL, all stages	LSA$_2$L$_2$ + HDMTX	24	Cranial if CNS involvement	HDMTX, IT	84	75	76
CCG502[55] (LSA$_2$L$_2$ v ADCOMP)	CCG, 1983-1990	LL	LSA$_2$L$_2$	24	Local Craniospinal if CNS involvement	IT	143	74	77
POG9404[56] (HDMTX, yes v no)	POG, 1996-2000	T-ALL and T-LL	Dana-Farber backbone	24	Cranial	IT ± HDMTX, cranial RT	137	85	NA
COG5941[57]	COG, 1994-1997	LL, advanced stages	Condensed	12	Cranial if CNS involvement	IT, HDMTX	85 (91% T-LL)	78	85
BFM86[4]	BFM, 1986-1990	LL, all stages	NHL-BFM-non-B	24	Cranial	IT, HDMTX, cranial RT (stage III/IV)	63 (91% T-LL)	84	88
BFM90[51]	BFM, 1990-1995	LL, all stages	NHL-BFM-non-B	24	Cranial	IT, HDMTX, cranial RTX (stage III/IV)	136 (81% T-LL)	90	92
BFM95[55]	BFM, 1995-2001	LL, all stages	NHL-BFM-non-B	24	Cranial if CNS involvement	IT, HDMTX	198 (73% T-LL)	80	86
CLG58881[54]	EORTC, 1989-1998	T-LL	NHL-BFM-non-B	24	No	IT, HDMTX	119	77.5	86
LMT96[58]	SFOP, 1997-2003	T-LL	Modified BFM	18-24	Cranial if CNS involvement	IT, HDMTX	79	85	89
AIEOP92[59]	AEIOP, 1992-1997	LL, all stages	LSA$_2$L$_2$	24	Cranial if CNS involvement	IT, HDMTX	55 (85% T-LL)	69	74
COGA5971[60] (CCG/ALL v NHL/BFM95; intensification: yes v no)	COG, 2000-2005	LL, advanced stages	Modified BFM	24	Cranial if CNS involvement	IT ± HDMTX	266 (86% T-LL)	82	85
EuroLb02[61] (dexamethasone v prednisone)	EICNHL, 2003-2008	LL, all stages	NHL-BFM90	24 v 18	Cranial if CNS involvement	IT, HDMTX	319 (78%)	81	NA

Abbreviations: ADCOMP, cyclophosphamide, vincristine, methotrexate, prednisone, daunorubicin, asparaginase, cytarabine; AEIOP, Italian Association of Pediatric Hematology and Oncology; ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Munster; B-LL, B-cell lymphoblastic lymphoma; CCG, Children's Cancer Group; COG, Children's Oncology Group; COMP, cyclophosphamide, vincristine, methotrexate, and prednisone; EFS, event-free survival; EICNHL, European Intergroup for Childhood Non-Hodgkin Lymphoma; EORTC, European Organisation for Research and Treatment of Cancer; HDMTX, high-dose methotrexate; IGR, Institut Gustave Roussy; IT, intrathecal injection; LL, lymphoblastic lymphoma; LMT, Lymphomes Malins T; LSA$_2$L$_2$, protocol of MSKCC; MSKCC, New York Memorial Sloan-Kettering Cancer Center; NA, not available; NHL, non-Hodgkin lymphoma; OS, overall survival; POG, Pediatric Oncology Group; RT, radiation therapy; SFOP, Société Francaise d'Oncologie Pédiatrique; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma.

moreover, by difficulties in obtaining appropriate material for immunophenotypic and molecular characterization. MDD and MRD can be studied using polymerase chain reaction (PCR) –based methods, molecular techniques, or flow cytometry in ALL. MDD measured by flow cytometry in a series of 99 T-LLs was present in two thirds of patients without cytologic BM involvement.[10] Interestingly, there was good correlation in paired BM and blood samples. High level of MDD was associated with a higher risk of hematologic relapses but not with local relapse. Further studies are needed to confirm the possibility of stratifying treatment on MDD and MRD in LL, as is already being done in ALL. Several biologic characteristics considered of prognostic relevance in T-LL have been described; in the BFM series,[65] loss of heterozygosity (LOH) on chromosome 6q (LOH6q; 12% of patients) was significantly associated with poorer outcome (EFS, 27% ± 9% v 86% ± 3% if no LOH6q), whereas the presence of NOTCH1 mutations (60% of patients) was associated with favorable outcome (EFS, 84% ± 5% v 66% ± 7% for no NOTCH1 mutations). NOTCH1 mutations and LOH6q16 were almost mutually exclusive. In a French series[66] studying FLASH deletion on chromosome 6q, TCR rearrangements, and NOTCH1/FBXW7 mutations, the latter was the only independent prognostic factors identified by multivariable analysis (EFS, 96% ± 0.04 v 45% ± 0.13 for presence v absence of mutations; P < .01). Finally, the prognostic value of RAS/PTEN alteration and absence of biallelic TCR-γ deletion also warrants evaluation in T-LL, by extrapolation from T-cell ALL.

With intensive first-line treatment, refractory disease or relapse occurs in 10% to 20% of patients. Relapse is mostly local in mediastinal T-LL. The outcome is dismal, with a cure rate of generally less than 30%.[67-69] In LL, there is a clear indication for an allograft if a second CR is achieved.[40] However, the difficulty of obtaining a second CR emphasizes the need for new treatments. So far, new agents for T-LL such as nelarabine[69] or clofarabine[70] have demonstrated limited effectiveness. Blinatumomab, a bi-specific CD19/CD3 antibody, may be promising for B-LL.

ALCL

Two forms of ALCL have been described—systemic and cutaneous ALCL. Systemic ALCL is characterized by peripheral, mediastinal, or intra-abdominal lymph node involvement, frequently associated with "B" symptoms and extranodal disease. A translocation resulting in the fusion of the anaplastic lymphoma kinase (ALK) gene to one of several partners can be detected in more than 90% of patients.

Primary cutaneous ALCLs usually lack ALK translocations and belong to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders, a group that also includes lymphomatoid papulosis. These entities remain confined to skin and usually carry an excellent prognosis after surgical resection without systemic therapy.

ALCLs express CD30 and, in most cases, EMA and cytotoxic molecules such as TIA-1, granzyme B, or perforin. Most patients express at least one T-cell antigen and exhibit clonal rearrangement of the T-cell receptor. Several histologic subtypes have been described including the common, small-cell, lymphohistiocytic, Hodgkin-like, and composite patterns.[71] The most common ALK fusion protein is nucleophosmin (NPM)-ALK resulting from the t(2;5) translocation. Several other partners can be involved. Most fusion products can be detected using fluorescent in situ hybridization, reverse transcriptase PCR, or immunohistochemistry.[71] These translocations induce constitutive phosphorylation of ALK that activates multiple pathways such JAK/STAT3, AKT/PI3K, and RAS/ERK, leading to growth factor–independent cell proliferation and inhibition of apoptosis.

In previous therapeutic studies with diverse first-line chemotherapy regimens in terms of duration of treatment and the number and cumulative doses of drugs, similar EFS rates of approximately 65% to 75% have been achieved in children and adolescents (Table 4).[72-79] Most pediatric groups now treat patients according to the ALCL99 protocol, a chemotherapy regimen derived from the NHL-BFM-B regimen, with MTX 3 g/m^2 in a 3-hour infusion and without IT therapy.[73]

One of the unique features of ALCL compared with other pediatric NHL is its sensitivity to chemotherapy after recurrence, leading to a survival rate of more than 90% in the recent ALCL99 study.[73,80-83] Several strategies, including reinduction chemotherapy followed by autologous or allogeneic hematopoietic stem-cell transplantation or weekly vinblastine, have been successful. The efficacy of vinblastine, initially shown in a small series of patients with multiple relapses,[83] was confirmed in the European ALCL relapse study. An interim analysis in August 2011 showed an 87% 2-year EFS rate in a small series of

Protocol	Study Group and Period of Study	Treatment Strategy	Treatment Duration (months)	No. of Patients	3- to 5-Year EFS (%)	3- to 5-Year OS (%)
HM89-91[72]	SFOP, 1989-1997	B-cell regimen (COPADM + maintenance)	7-8	82	66	83
NHL-BFM90[74]	BFM, 1990-1995	B-cell regimen (BFM-B)	2-5	89	76	—
NHL 9000 and 9602[75]	UKCCSG, 1990-1998	B-cell regimen (LMB)	4-5	72	59	65
LNH92[76]	AEIOP, 1993-1997	T-cell regimen	24	34	65	85
POG9315[78]	POG, 1994-2000	APO + randomization of HDMTX and HDAra-C	12	86	72	88
CCG5941[78]	CCG, 1996-2001	Compressed T-cell regimen	11	86	68	80
ALCL99[73,80]	EICNHL, 1999-2006	B-cell regimen (BFM-B) + randomization of vinblastine	4-12	352	73	92
ANHL0131[79]	COG, 2004-2008	APO + randomization of vinblastine	12	125	74	84

Table 4. Results of the Main Series of Pediatric ALCL

Abbreviations: AEIOP, Italian Association of Pediatric Hematology and Oncology; ALCL, anaplastic large-cell lymphoma; APO, doxorubicin, prednisone, and vincristine; BFM, Berlin-Frankfurt-Munster; CCG, Children's Cancer Group; COG, Children's Oncology Group; COPADM, vincristine, methylprednisolone, methotrexate, leucovorin, cyclophosphamide, and doxorubicin; EFS, event-free survival; EICNHL, European Intergroup for Childhood Non-Hodgkin Lymphoma; HDAra-C, high-dose cytarabine; HDMTX, high-dose methotrexate; LMB, Lymphomes Malins B; NHL, non-Hodgkin lymphoma; OS, overall survival; POG, Pediatric Oncology Group; SFOP, Société Française d'Oncologie Pédiatrique; UKCCSG, United Kingdom Children's Cancer Study Group.

patients with a late relapse (median follow-up, 34 months) treated with vinblastine.[84] The role of weekly vinblastine maintenance in first-line treatment has also been investigated in the ALCL99 trial (addition of vinblastine to each course and as maintenance for a total treatment duration of 12 months) and in the COG ANHL0131 trial (vincristine replaced by weekly vinblastine in the doxorubicin, prednisone, and vincristine regimen), but no reduction in risk of relapse could be demonstrated with this duration of treatment.[79,80]

Several prognostic factors associated with an increased risk of failure have been identified in ALCL, including the presence of mediastinal or visceral involvement and skin lesions,[85] histologic lymphohistiocytic and small-cell variant patterns, and the detection of MDD by reverse transcriptase PCR for NPM-ALK in blood or BM.(positive in approximately 50% of patients, whereas < 15% of patients exhibit cytologically detectable BM disease).[71,75,76,86,87] More recently, new parameters such as the persistence of positive MRD after 4 weeks[88] of treatment and low production of anti-ALK titers were also identified. In a series of 128 patients, MDD and antibody titer allowed stratification into the following three biologic risk groups[89]: high risk with MDD-positive status and low antibody titer (20% of patients; 5-year PFS, 28%), low risk with MDD-negative status and a high antibody titer (31% of patients; 5-year PFS, 93%), and intermediate risk including the remaining patients (48% of patients; 5-year PFS, 68%). Validation of this prognostic classification is planned in the future EICNHL clinical study.

Accumulating evidence indicates that the immune system plays a major role in both the pathogenesis and final control of ALK-positive ALCL.[90] Antibodies against ALK and cytotoxic T-cell and CD4 T-helper responses to ALK have been detected in patients with ALK-positive ALCL both at diagnosis and during remission, with a significant inverse correlation between ALK antibody titers and incidence of relapse.[91] The presence of germline monoallelic mutations of the perforin gene has been demonstrated in ALCL, suggesting that impairment of cytotoxic lymphocyte function may predispose to ALCL.[92]

Interestingly, vinblastine is a potent immunomodulator that enhances anticancer immune response by stimulating dendritic cell (DC) function. In vitro, vinblastine induces the production of IL-1α, IL-6, and IL-12; increases surface expression of CD40, CD80, CD86, and major histocompatibility complex class II; and enhances T-cell stimulatory capacity of DCs.[93] Vinblastine is speculated to release the high mobility group box 1 protein,[94] a major molecule involved in DC stimulation and immunogenic cell death.

Several new drugs have recently been implemented in the treatment of ALCL. Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody conjugated to the antimicrotubule cytotoxic monomethyl auristatin-E. A study of 58 patients with relapsed/refractory ALCL (ALK positive, n = 16) treated with BV reported an objective response rate of 86% with a median duration of 12.6 months.[95] After these results, BV was approved by the US Food and Drug Administration and European Medical Agency for the treatment of systemic ALCL after failure of at least one chemotherapy regimen in adults.

ALK inhibitors such as crizotinib, an ALK/MET inhibitor, are also promising drugs. Crizotinib is now approved by the US Food and Drug Administration and European Medical Agency for the treatment

of ALK-positive lung cancers. The results in ALCL are also encouraging with seven CRs in nine patients with relapsed/refractory ALCL included in a pediatric phase I trial of crizotinib.[96] The same results were obtained with a response rate of 91% in 11 patients with ALK-positive resistant/refractory adult lymphoma.[97] Given these results, the COG is currently investigating the feasibility of combining BV or crizotinib with ALCL99 chemotherapy in children with newly diagnosed stage II to IV ALCL (ClinicalTrials.gov identifier: NCT01979536), whereas the EICNHL is planning a randomized trial with risk stratification based on MDD and antibody levels, aimed at evaluating the efficacy of adding crizotinib to ALCL99 in first-line therapy for intermediate- and high-risk ALCL and comparing weekly vinblastine to ALCL99 in low- and intermediate-risk disease.

CONCLUSION

Thanks to better recognition of the diseases and to national and international collaborations, the vast majority of children and adolescents with NHL will be cured using chemotherapy adapted to specific lymphoma subtype and disease extent. However, contemporary treatments are often associated with acute myelosuppressive and GI toxicities that not only hamper quality of life, but can also be life threatening. However, for many children, few long-term toxicities are anticipated because of low cumulative chemotherapy doses and elimination of radiation therapy.

The therapeutic strategies and treatment intensity vary considerably between pediatric and adult approaches for similar NHL subtypes. The lack of uniform criteria for staging and the limited data concerning age-related biologic characteristics of each subtype preclude understanding of the impact of these differences on patient outcomes. Defining new prognostic factors will facilitate the development of better risk-adapted strategies. New treatments including antibodies and/or targeted therapies hold promise for advancing outcomes in children with refractory/relapsed lymphoma. It is improbable that they will cure NHL on their own, but their combination with chemotherapy may allow reduction in treatment intensity and chemotherapy-related toxicities. Except for high-risk patients who require further therapeutic improvements, the challenge over the coming years will be to maintain already high cure rates while minimizing acute and long-term toxicity. This effort will require further pediatric international collaboration as well as partnerships with adult lymphoma groups.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Provision of study materials or patients: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Swerdlow S, Campo E, Harris N, et al: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4). Geneva, Switzerland, WHO, 2008

2. Percy C, Smith M, Linet M: Lymphomas and reticuloendothelial neoplasms, in Ries L, Smith M, Gurney J (eds): Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995. Bethesda, MD, National Cancer Institute, SEER Program, 1999, pp 35-50

3. Burkhardt B, Zimmermann M, Oschlies I, et al: The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol 131:39-49, 2005

4. Reiter A, Schrappe M, Parwaresch R, et al: Non-Hodgkin's lymphomas of childhood and adolescence: Results of a treatment stratified for biologic subtypes and stage—A report of the Berlin-Frankfurt-Münster Group. J Clin Oncol 13:359-372, 1995

5. Bienemann K, Burkhardt B, Modlich S, et al: Promising therapy results for lymphoid malignancies in children with chromosomal breakage syndromes (ataxia telangiectasia or Nijmegen-breakage syndrome): a retrospective survey. Br J Haematol 155:468-476, 2011

6. Sandlund JT, Hudson MM, Kennedy W, et al: Pilot study of modified LMB-based therapy for children with ataxia-telangiectasia and advanced stage high grade mature B-cell malignancies. Pediatr Blood Cancer 61:360-362, 2014

7. Neven B, Mamessier E, Bruneau J, et al: A Mendelian predisposition to B-cell lymphoma caused by IL-10R deficiency. Blood 122:3713-3722, 2013

8. Wimmer K, Kratz CP, Vasen HF, et al: Diagnostic criteria for constitutional mismatch repair deficiency syndrome: Suggestions of the European consortium "care for CMMRD" (C4CMMRD). J Med Genet 51:355-365, 2014

9. Mussolin L, Pillon M, d'Amore ES, et al: Minimal disseminated disease in high-risk Burkitt's lymphoma identifies patients with different prognosis. J Clin Oncol 29:1779-1784, 2011

10. Coustan-Smith E, Sandlund JT, Perkins SL, et al: Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: A report from the Children's Oncology Group. J Clin Oncol 27:3533-3539, 2009

11. Shiramizu B, Goldman S, Kusao I, et al: Minimal disease assessment in the treatment of children and adolescents with intermediate-risk (stage III/IV) B-cell non-Hodgkin lymphoma: A Children's Oncology Group report. Br J Haematol 153:758-763, 2011

11a. Rosolen A, Perkins SL, Pinkerton CR, et al: Revised International Pediatric Non-Hodgkin Lymphoma Staging System. J Clin Oncol [epub ahead of print on May 4, 2015]

11b. Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol [epub ahead of print on May 4, 2015]

12. Anderson JR, Jenkin RD, Wilson JF, et al: Long-term follow-up of patients treated with COMP or LSA2L2 therapy for childhood non-Hodgkin's lymphoma: A report of CCG-551 from the Children's Cancer Group. J Clin Oncol 11:1024-1032, 1993

13. Patte C, Philip T, Rodary C, et al: High survival rate in advanced-stage B-cell lymphomas and leukemias without CNS involvement with a short intensive polychemotherapy: Results from the French Pediatric Oncology Society of a randomized trial of 216 children. J Clin Oncol 9:123-132, 1991

14. Patte C, Auperin A, Michon J, et al: The Société Française d'Oncologie Pédiatrique LMB89 protocol: Highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood 97:3370-3379, 2001

15. Gerrard M, Cairo MS, Weston C, et al: Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: Results of the FAB/LMB 96 international study. Br J Haematol 141:840-847, 2008

16. Patte C, Auperin A, Gerrard M, et al: Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: It is possible to reduce treatment for the early responding patients. Blood 109:2773-2780, 2007

17. Cairo MS, Gerrard M, Sposto R, et al: Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 109:2736-2743, 2007

18. Reiter A, Schrappe M, Tiemann M, et al: Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood 94:3294-3306, 1999

19. Woessmann W, Seidemann K, Mann G, et al: The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: A report of the BFM Group Study NHL-BFM95. Blood 105:948-958, 2005

20. Tsurusawa M, Mori T, Kikuchi A, et al: Improved treatment results of children with B-cell non-Hodgkin lymphoma: A report from the Japanese Pediatric Leukemia/Lymphoma Study Group B-NHL03 study. Pediatr Blood Cancer 61:1215-1221, 2014

21. Cairo MS, Sposto R, Gerrard M, et al: Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age (≥ 15 years), are associated with an increased risk of treatment failure in children and adolescents with mature B-cell non-Hodgkin's lymphoma: Results of the FAB LMB 96 study. J Clin Oncol 30:387-393, 2012

22. Harif M, Barsaoui S, Benchekroun S, et al: Treatment of B-cell lymphoma with LMB modified protocols in Africa: Report of the French-African Pediatric Oncology Group (GFAOP). Pediatr Blood Cancer 50:1138-1142, 2008

23. Traoré F, Coze C, Atteby JJ, et al: Cyclophosphamide monotherapy in children with Burkitt lymphoma: A study from the French-African Pediatric Oncology Group (GFAOP). Pediatr Blood Cancer 56:70-76, 2011

24. Reiter A, Klapper W: Recent advances in the understanding and management of diffuse large B-cell lymphoma in children. Br J Haematol 142:329-347, 2008

25. Oschlies I, Klapper W, Zimmermann M, et al: Diffuse large B-cell lymphoma in pediatric patients belongs predominantly to the germinal-center type B-cell lymphomas: A clinicopathologic analysis of cases included in the German BFM (Berlin-Frankfurt-Munster) Multicenter Trial. Blood 107:4047-4052, 2006

26. Miles RR, Raphael M, McCarthy K, et al: Pediatric diffuse large B-cell lymphoma demonstrates a high proliferation index, frequent c-Myc protein expression, and a high incidence of germinal center subtype: Report of the French-American-British (FAB) international study group. Pediatr Blood Cancer 51:369-374, 2008

27. Poirel HA, Cairo MS, Heerema NA, et al: Specific cytogenetic abnormalities are associated with a significantly inferior outcome in children and adolescents with mature B-cell non-Hodgkin's lymphoma: Results of the FAB/LMB 96 international study. Leukemia 23:323-331, 2009

28. Gerrard M, Waxman IM, Sposto R, et al: Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood 121:278-285, 2013

29. Oschlies I, Burkhardt B, Salaverria I, et al: Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. Haematologica 96:262-268, 2011

30. Meinhardt A, Burkhardt B, Zimmermann M, et al: Phase II window study on rituximab in newly diagnosed pediatric mature B-cell non-Hodgkin's lymphoma and Burkitt leukemia. J Clin Oncol 28:3115-3121, 2010

31. Goldman S, Smith L, Anderson JR, et al: Rituximab and FAB/LMB 96 chemotherapy in children with stage III/IV B-cell non-Hodgkin lymphoma: A Children's Oncology Group report. Leukemia 27:1174-1177, 2013

32. Goldman S, Smith L, Galardy P, et al: Rituximab with chemotherapy in children and adolescents with central nervous system and/or bone marrow-positive Burkitt lymphoma/leukaemia: A Children's Oncology Group Report. Br J Haematol 167:394-401, 2014

33. Dunleavy K, Pittaluga S, Maeda LS, et al: Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 368:1408-1416, 2013

34. Mussolin L, Pillon M, Conter V, et al: Prognostic role of minimal residual disease in mature B-cell acute lymphoblastic leukemia of childhood. J Clin Oncol 25:5254-5261, 2007

35. Fujita N, Mori T, Mitsui T, et al: The role of hematopoietic stem cell transplantation with relapsed or primary refractory childhood B-cell non-Hodgkin lymphoma and mature B-cell leukemia: A retrospective analysis of enrolled cases in Japan. Pediatr Blood Cancer 51:188-192, 2008

36. Anoop P, Sankpal S, Stiller C, et al: Outcome of childhood relapsed or refractory mature B-cell non-Hodgkin lymphoma and acute lymphoblastic leukemia. Leuk Lymphoma 53:1882-1888, 2012

37. Jourdain A, Auperin A, Minard-Colin V, et al: Outcome and prognostic factors of relapse in children and adolescents with mature B-cell lymphoma and leukemia treated in 3 consecutive prospective LMB protocols. Haematologica [epub ahead of print on February 27, 2015]

38. Gentet JC, Patte C, Quintana E, et al: Phase II study of cytarabine and etoposide in children with refractory or relapsed non-Hodgkin's lymphoma: A study of the French Society of Pediatric Oncology. J Clin Oncol 8:661-665, 1990

39. Griffin TC, Weitzman S, Weinstein H, et al: A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. Pediatr Blood Cancer 52:177-181, 2009

40. Gross TG, Hale GA, He W, et al: Hematopoietic stem cell transplantation for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. Biol Blood Marrow Transplant 16:223-230, 2010

41. Goebeler M, Viardot A, Noppeney R, et al: Blinatumomab (CD3/CD19 Bite (R) Antibody) results in a high response rate in patients with relapsed non-Hodgkin lymphoma (NHL) including mantle cell lymphoma (MCL) and diffuse large B cell lymphoma (DLBCL). Ann Oncol 22:190, 2011

42. Younes A, Thieblemont C, Morschhauser F, et al: Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: A non-randomised, phase 1b study. Lancet Oncol 15:1019-1026, 2014

43. Sander S, Calado DP, Srinivasan L, et al: Synergy between PI3K signaling and MYC in Burkitt lymphomagenesis. Cancer Cell 22:167-179, 2012

44. Love C, Sun Z, Jima D, et al: The genetic landscape of mutations in Burkitt lymphoma. Nat Genet 44:1321-1325, 2012

45. Richter J, Schlesner M, Hoffmann S, et al: Recurrent mutation of the ID3 gene in Burkitt lymphoma identified by integrated genome, exome and transcriptome sequencing. Nat Genet 44:1316-1320, 2012

46. Schmitz R, Young RM, Ceribelli M, et al: Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. Nature 490:116-120, 2012

47. Greenough A, Dave SS: New clues to the molecular pathogenesis of Burkitt lymphoma revealed through next-generation sequencing. Curr Opin Hematol 21:326-332, 2014

48. Ducassou S, Ferlay C, Bergeron C, et al: Clinical presentation, evolution, and prognosis of precursor B-cell lymphoblastic lymphoma in trials LMT96, EORTC 58881, and EORTC 58951. Br J Haematol 152:441-451, 2011

49. Oschlies I, Burkhardt B, Chassagne-Clement C, et al: Diagnosis and immunophenotype of 188 pediatric lymphoblastic lymphomas treated within a randomized prospective trial: Experiences and preliminary recommendations from the European childhood lymphoma pathology panel. Am J Surg Pathol 35:836-844, 2011

50. Mora J, Filippa DA, Qin J, et al: Lymphoblastic lymphoma of childhood and the LSA2-L2 protocol: The 30-year experience at Memorial-Sloan-Kettering Cancer Center. Cancer 98:1283-1291, 2003

51. Reiter A, Schrappe M, Ludwig WD, et al: Intensive ALL-type therapy without local radiotherapy provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: A BFM group report. Blood 95:416-421, 2000

52. Burkhardt B, Woessmann W, Zimmermann M, et al: Impact of cranial radiotherapy on central nervous system prophylaxis in children and adolescents with central nervous system-negative stage III or IV lymphoblastic lymphoma. J Clin Oncol 24:491-499, 2006

53. Patte C, Kalifa C, Flamant F, et al: Results of the LMT81 protocol, a modified LSA2L2 protocol with high dose methotrexate, on 84 children with non-B-cell (lymphoblastic) lymphoma. Med Pediatr Oncol 20:105-113, 1992

54. Uyttebroeck A, Suciu S, Laureys G, et al: Treatment of childhood T-cell lymphoblastic lymphoma according to the strategy for acute lymphoblastic leukaemia, without radiotherapy: Long term results of the EORTC CLG 58881 trial. Eur J Cancer 44:840-846, 2008

55. Tubergen DG, Krailo MD, Meadows AT, et al: Comparison of treatment regimens for pediatric lymphoblastic non-Hodgkin's lymphoma: A Chil-

dren's Cancer Group study. J Clin Oncol 13:1368-1376, 1995

56. Asselin BL, Devidas M, Wang C, et al: Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: A randomized study by the Children's Oncology Group (POG 9404). Blood 118:874-883, 2011

57. Abromowitch M, Sposto R, Perkins S, et al: Shortened intensified multi-agent chemotherapy and non-cross resistant maintenance therapy for advanced lymphoblastic lymphoma in children and adolescents: Report from the Children's Oncology Group. Br J Haematol 143:261-267, 2008

58. Bergeron C, Celine S, Pacquement H, et al: Childhood T-cell lymphoblastic lymphoma (TLL) results of the SFOP LMT96 strategy. Pediatr Blood Cancer 46:867a, 2006 (abstr)

59. Pillon M, Piglione M, Garaventa A, et al: Long-term results of AIEOP LNH-92 protocol for the treatment of pediatric lymphoblastic lymphoma: A report of the Italian Association of Pediatric Hematology and Oncology. Pediatr Blood Cancer 53:953-959, 2009

60. Termuhlen AM, Smith LM, Perkins SL, et al: Disseminated lymphoblastic lymphoma in children and adolescents: Results of the COG A5971 trial—A report from the Children's Oncology Group. Br J Haematol 162:792-801, 2013

61. Reiter A, Burkhardt B, Zimmermann M: Results of the European intergroup trial EUROLB02 on lymphoblastic lymphoma (LBL) in children/adolescents. Br J Haematol 159:1-73, 2012 (suppl)

62. Amylon MD, Shuster J, Pullen J, et al: Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: A Pediatric Oncology Group study. Leukemia 13:335-342, 1999

63. Duval M, Suciu S, Ferster A, et al: Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: Results of a randomized European Organisation for Research and Treatment of Cancer—Children's Leukemia Group phase 3 trial. Blood 99:2734-2739, 2002

64. Sandlund JT, Pui CH, Zhou Y, et al: Results of treatment of advanced-stage lymphoblastic lymphoma at St Jude Children's Research Hospital from 1962 to 2002. Ann Oncol 24:2425-2429, 2013

65. Bonn BR, Rohde M, Zimmermann M, et al: Incidence and prognostic relevance of genetic variations in T-cell lymphoblastic lymphoma in childhood and adolescence. Blood 121:3153-3160, 2013

66. Callens C, Baleydier F, Lengline E, et al: Clinical impact of NOTCH1 and/or FBXW7 mutations, FLASH deletion, and TCR status in pediatric T-cell lymphoblastic lymphoma. J Clin Oncol 30:1966-1973, 2012

67. Burkhardt B, Reiter A, Landmann E, et al: Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: A report from the Berlin-Frankfurt-Muenster group. J Clin Oncol 27:3363-3369, 2009

68. Mitsui T, Mori T, Fujita N, et al: Retrospective analysis of relapsed or primary refractory childhood lymphoblastic lymphoma in Japan. Pediatr Blood Cancer 52:591-595, 2009

69. Dunsmore KP, Devidas M, Linda SB, et al: Pilot study of nelarabine in combination with intensive chemotherapy in high-risk T-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. J Clin Oncol 30:2753-2759, 2012

70. Cooper TM, Razzouk BI, Gerbing R, et al: Phase I/II trial of clofarabine and cytarabine in chil-

dren with relapsed/refractory acute lymphoblastic leukemia (AAML0523): A report from the Children's Oncology Group. Pediatr Blood Cancer 60:1141-1147, 2013

71. Lamant L, McCarthy K, d'Amore E, et al: Prognostic impact of morphologic and phenotypic features of childhood ALK-positive anaplastic large-cell lymphoma: Results of the ALCL99 study. J Clin Oncol 29:4669-4676, 2011

72. Brugières L, Deley MC, Pacquement H, et al: CD30(+) anaplastic large-cell lymphoma in children: Analysis of 82 patients enrolled in two consecutive studies of the French Society of Pediatric Oncology. Blood 92:3591-3598, 1998

73. Brugières L, Le Deley MC, Rosolen A, et al: Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: Results of a randomized trial of the EICNHL Group. J Clin Oncol 27:897-903, 2009

74. Seidemann K, Tiemann M, Schrappe M, et al: Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: A report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood 97:3699-3706, 2001

75. Williams DM, Hobson R, Imeson J, et al: Anaplastic large cell lymphoma in childhood: Analysis of 72 patients treated on The United Kingdom Children's Cancer Study Group chemotherapy regimens. Br J Haematol 117:812-820, 2002

76. Rosolen A, Pillon M, Garaventa A, et al: Anaplastic large cell lymphoma treated with a leukemia-like therapy: Report of the Italian Association of Pediatric Hematology and Oncology (AIEOP) LNH-92 protocol. Cancer 104:2133-2140, 2005

77. Laver JH, Kraveka JM, Hutchison RE, et al: Advanced-stage large-cell lymphoma in children and adolescents: Results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen—A Pediatric Oncology Group phase III trial. J Clin Oncol 23:541-547, 2005

78. Lowe EJ, Sposto R, Perkins SL, et al: Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents: Final results of Children's Cancer Group Study 5941. Pediatr Blood Cancer 52:335-339, 2009

79. Alexander S, Kraveka JM, Weitzman S, et al: Advanced stage anaplastic large cell lymphoma in children and adolescents: Results of ANHL0131, a randomized phase III trial of APO versus a modified regimen with vinblastine—A report from the Children's Oncology Group. Pediatr Blood Cancer 61:2236-2242, 2014

80. Le Deley M-C, Rosolen A, Williams DM, et al: Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: Results of the randomized ALCL99-vinblastine trial. J Clin Oncol 28:3987-3993, 2010

81. Brugières L, Quartier P, Le Deley MC, et al: Relapses of childhood anaplastic large-cell lymphoma: Treatment results in a series of 41 children—A report from the French Society of Pediatric Oncology. Ann Oncol 11:53-58, 2000

82. Woessmann W, Zimmermann M, Lenhard M, et al: Relapsed or refractory anaplastic large-cell lymphoma in children and adolescents after Berlin-Frankfurt-Muenster (BFM)-type first-line therapy: A BFM-group study. J Clin Oncol 29:3065-3071, 2011

83. Brugières L, Pacquement H, Le Deley MC, et al: Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: A report from the French Society of Pediatric Oncology. J Clin Oncol 27:5056-5061, 2009

84. Woessmann W, Brugières L, Roselen A, et al: Risk-adapted therapy for patients with relapsed or refractory ALCL: Interim results of the prospective EICNHL Trial ALCL-Relapse. Br J Haematol 159:41, 2012 (suppl 1)

85. Le Deley MC, Reiter A, Williams D, et al: Prognostic factors in childhood anaplastic large cell lymphoma: Results of a large European intergroup study. Blood 111:1560-1566, 2008

86. Damm-Welk C, Busch K, Burkhardt B, et al: Prognostic significance of circulating tumor cells in bone marrow or peripheral blood as detected by qualitative and quantitative PCR in pediatric NPM-ALK-positive anaplastic large-cell lymphoma. Blood 110:670-677, 2007

87. Mussolin L, Pillon M, d'Amore ES, et al: Prevalence and clinical implications of bone marrow involvement in pediatric anaplastic large cell lymphoma. Leukemia 19:1643-1647, 2005

88. Damm-Welk C, Mussolin L, Zimmermann M, et al: Early assessment of minimal residual disease identifies patients at very high relapse risk in NPM-ALK-positive anaplastic large-cell lymphoma. Blood 123:334-337, 2014

89. Mussolin L, Damm-Welk C, Pillon M, et al: Use of minimal disseminated disease and immunity to NPM-ALK antigen to stratify ALK-positive ALCL patients with different prognosis. Leukemia 27:416-422, 2013

90. Ait-Tahar K, Cerundolo V, Banham AH, et al: B and CTL responses to the ALK protein in patients with ALK-positive ALCL. Int J Cancer 118:688-695, 2006

91. Ait-Tahar K, Damm-Welk C, Burkhardt B, et al: Correlation of the autoantibody response to the ALK oncoantigen in pediatric anaplastic lymphoma kinase-positive anaplastic large cell lymphoma with tumor dissemination and relapse risk. Blood 115:3314-3319, 2010

92. Ciambotti B, Mussolin L, d'Amore ES, et al: Monoallelic mutations of the perforin gene may represent a predisposing factor to childhood anaplastic large cell lymphoma. J Pediatr Hematol Oncol 36:e359-e365, 2014

93. Tanaka H, Matsushima H, Mizumoto N, et al: Classification of chemotherapeutic agents based on their differential in vitro effects on dendritic cells. Cancer Res 69:6978-6986, 2009

94. Tanaka H, Matsushima H, Nishibu A, et al: Dual therapeutic efficacy of vinblastine as a unique chemotherapeutic agent capable of inducing dendritic cell maturation. Cancer Res 69:6987-6994, 2009

95. Pro B, Advani R, Brice P, et al: Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: Results of a phase II study. J Clin Oncol 30:2190-2196, 2012

96. Mossé YP, Lim MS, Voss SD, et al: Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A Children's Oncology Group phase 1 consortium study. Lancet Oncol 14:472-480, 2013

97. Gambacorti Passerini C, Farina F, Stasia A, et al: Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J Natl Cancer Inst 106:378, 2014

Affiliations

Véronique Minard-Colin, Laurence Brugières, Anne Auperin, Marie-Cécile Le Deley, and Catherine Patte, Institut Gustave Roussy, Villejuif; Martine Raphael, Centre National de la Recherche Scientifique UMR 8126, Université Paris Sud; Elizabeth Macintyre, Université Paris Descartes Sorbonne Cité, Institut Necker-Enfants Malades, Institut National de Recherche Médicale U1151, and Assistance Publique–Hôpitaux de Paris, Hôpital Necker Enfants-Malades, Paris; Laurence Lamant, Institut Universitaire du Cancer Toulouse Oncopole and Université Paul-Sabatier, Toulouse, France; Alfred Reiter, Wilhelm Woessmann, and Christine Damm-Welk, Justus-Liebig-University Giessen, Giessen; Birgit Burkhardt, Children University Hospital, Münster; Martin Zimmerman, Medizinische Hochschule, Hannover; Wolfram Klapper, Christian-Albrechts-University Kiel, Kiel, Germany; Mitchell S. Cairo, New York Medical College, Valhalla, NY; Thomas G. Gross, National Cancer Institute, Bethesda, MD; John T. Sandlund, St Jude Children's Research Hospital and University of Tennessee Health Science Center, College of Medicine, Memphis, TN; Sherrie L. Perkins, University of Utah Health Sciences, Salt Lake City, UT; Denise Williams, Cambridge University Hospitals Foundation Trust, Cambridge, United Kingdom; Marta Pillon and Angelo Rosolen, University of Padova, Padova; Lara Mussolin, Istituto di Ricerca Pediatrico-Fondazione Cittàdella Speranza and University of Padua, Padua, Italy; Keizo Horibe, National Hospital Organization Nagoya Medical Center, Nagoya, Japan; and Hélène A. Poirel, Center for Human Genetics, Cliniques Universitaires Saint-Luc–Université Catholique de Louvain, Belgium, Brussels.

■ ■ ■

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Non-Hodgkin Lymphoma in Children and Adolescents: Progress Through Effective Collaboration, Current Knowledge, and Challenges Ahead

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Veronique Minard-Colin
No relationship to disclose

Laurence Brugières
No relationship to disclose

Alfred Reiter
No relationship to disclose

Mitchell S. Cairo
Consulting or Advisory Role: Sanofi
Speakers' Bureau: Sanofi

Thomas G. Gross
No relationship to disclose

Wilhem Woessmann
No relationship to disclose

Birgit Burkhardt
Consulting or Advisory Role: Roche, Janssen Pharmaceuticals
Travel, Accommodations, Expenses: EUSA Pharma

John T. Sandlund
No relationship to disclose

Denise Williams
Honoraria: Novo Nordisk (I)
Consulting or Advisory Role: Biogen Idec (I), Novo Nordisk (I)

Marta Pillon
No relationship to disclose

Keizo Horibe
No relationship to disclose

Anne Auperin
Travel, Accommodations, Expenses: Merck Serono

Marie-Cécile Le Deley
No relationship to disclose

Martin Zimmerman
No relationship to disclose

Sherrie L. Perkins
No relationship to disclose

Martine Raphael
No relationship to disclose

Laurence Lamant
No relationship to disclose

Wolfram Klapper
Honoraria: F. Hoffmann-La Roche, Novartis, Janssen Pharmaceuticals
Consulting or Advisory Role: F. Hoffmann-La Roche (Inst), Novartis (Inst), Janssen Pharmaceuticals (Inst)
Research Funding: F. Hoffmann-La Roche (Inst), Novartis (Inst), Janssen Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: F. Hoffmann-La Roche, Novartis, Janssen Pharmaceuticals

Lara Mussolin
No relationship to disclose

Hélène A. Poirel
Travel, Accommodations, Expenses: Roche

Elizabeth Macintyre
Patents, Royalties, Other Intellectual Property: Shared EuroClonality patent

Christine Damm-Welk
No relationship to disclose

Angelo Rosolen
No relationship to disclose

Catherine Patte
No relationship to disclose